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Risk of carcinoma in women with ovarian endometrioma

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1. ABSTRACT

Endometriosis affects an estimated 10% of women in the reproductive-age group. Here, we review current knowledge on molecular genesis of endometriosis-associated epithelial ovarian carcinoma (EOC). This article reviews the English language literature for biology, pathogenesis, and pathophysiological studies on endometriosis-associated EOC. Although endometriosis generally remains a benign condition, it demonstrates somatically acquired genetic alterations. Clear cell carcinoma (CCC) and endometrioid adenocarcinoma (EAC) are the most frequent types of EOC associated with endometriosis. Retrograde menstruation or ovarian hemorrhage carries highly pro-oxidant factors, such as iron, into the peritoneal cavity or ovarian endometrioma. CCC and EAC should be considered separately in studies of endometriosis-associated EOC. The repeated events of hemorrhage in endometriosis can contribute to carcinogenesis and progression via 3 major processes: 1) increasing oxidative stress promotes DNA methylation; 2) activating anti-apoptotic pathways supports tumor promotion; and 3) aberrant expression of stress signaling pathways contributes to tumor progression. This review summarizes recent advances in the understanding of epidemiology, carcinogenesis, pathogenesis, and pathophysiology of endometriosis-associated EOC; and a possible novel model is proposed.

2. INTRODUCTION

The present article reviews the English language literature for epidemiological, biological, pathogenetic and pathophysiological studies on endometriosis-associated epithelial ovarian carcinoma (EOC). We searched MEDLINE (PubMed) electronic databases for a 20-year period (1991-2010), combining the keywords "epidemiology" "etiology" "molecular genetics" "signaling" "pathogenesis" "clear cell carcinoma of the ovary" "endometrioid adenocarcinoma of the ovary" with "endometriosis-associated epithelial ovarian carcinoma". Several recent studies are discussed in the context of endometriosis-associated EOC biology. Additionally, references in each article were searched to identify potentially missed studies. Study selection is as follows. Studies that only categorized histologic subtype as serous and nonserous, without further classification of nonserous subtypes were excluded. Here, we discuss the understanding of epidemiology, carcinogenesis, pathogenesis, and pathophysiology and propose a promising novel model for development of endometriosis-associated EOC.

3. ENDOMETRIOSIS

3.1. Etiology and pathogenesis

Endometriosis is a common medical condition where endometrial tissue is present outside the uterine

cavity, preferentially in the cul-de-sac and on the ovary (1). It is a frequent disorder that commonly presents with infertility and pelvic pain (2). Endometriosis affects an estimated 10% of women in the reproductive-age group, rising to 30% to 50% in patients with infertility. Here, we review current knowledge suggesting that endometriosis might be viewed as a neoplastic process. An association between endometriosis and EOC has been accumulated by several studies including epidemiology, natural history, histopathology, morphometry, proteomics, genomics, and gene microarrays (2). Understanding the mechanisms of the development of endometriosis and elucidating its pathogenesis and pathophysiology are intrinsic to the prevention of endometriosis-associated EOC and the search for diagnostic classification, individualized treatments and effective therapies.

The pathogenesis of endometriosis is currently understood as being multifactorial. The precise etiology and pathogenesis of endometriosis is likely multifactorial, and it is generally considered to involve multiple genetic, environmental, inflammatory, immunological, and endocrine processes (2). There are several theories to explain their pathogenesis: retrograde transplantation of shed menstrual effluent (peritoneal implants), metaplasia of the mesothelium, or *in situ* development of Müllerian remnants in the rectovaginal area (deep invasive lesions). The implantation theory (3) and the coelomic metaplasia theory (4) are the most widely accepted pathogenesis of this disorder. Although retrograde menstruation has been shown in most women of reproductive age, only a portion of women develop endometriosis. Osuga showed a simplified view of the sequential steps with their relevant factors in the development of endometriosis (5). They include biological changes in eutopic endometrium, reduced apoptosis, increased attachment, invasion and growth, and changes in metabolic factors (5). On the other hand, Cho reported a case report of endometriosis in a patient with Rokitansky-Kuster-Hauser syndrome (6). Since this patient did not have a functioning endometrium, her endometrioma is assumed to have arisen from coelomic metaplasia. Recent studies, including the use of proteomics, genomics, and microarrays technologies, have contributed to the elucidation of the specific pathways to the formation of endometriosis.

3.2. Inflammatory process

Inflammation plays an important role in the pathogenesis of endometriosis, by allowing lesions to develop and progress. Retrograde menstruation or ovarian hemorrhage carries high concentrations of heme and iron into the peritoneal cavity or ovarian endometrioma. The recent work has reviewed on identifying the role of inflammatory response possibly through iron-mediated oxidative stress in the pathogenesis of endometriosis (7). The hormonally regulated lesions of endometriosis are actually characterized by pelvic inflammation that shows an increased number of activated peritoneal macrophages and elevation of growth factors, angiogenic factors and proinflammatory cytokines (1,8). These cytokines can cause unregulated mitotic division, growth and differentiation, migration or apoptosis (8). Activation of nuclear factor-kappa B (NF-kappaB), a pro-inflammatory transcription factor, is increased in peritoneal macrophages from patients with endometriosis when compared with controls (9). In addition to NF-kappaB activation, the PI3K-Akt and MAPK signaling pathways might be activated in human endometriotic lesions similar to malignant mechanisms (10).

Furthermore, Toll-like receptor (TLR)-dependent signaling possibly through iron redox status and oxidative stress may constitute a pivotal factor contributing to the extent of microbial stimuli or sterile inflammation in endometriosis. TLRs are considered to be critical components in the regulation of ascending bacterial pathogens (11). Khan *et al.*, found that the LPS concentration in peritoneal fluid was higher in women with endometriosis than in those without (12). They suggest that a substantial amount of LPS in peritoneal fluid is also involved in pelvic inflammation and may promote TLR4-mediated growth of endometriosis (12). The system such as TLR responds to infectious, non-self agents, or some self components, thereby inducing an inflammatory response (12). TLR4 might be critical to the signaling of a variety of "danger signals", which includes heat shock proteins (HSPs), S100, fibronectin, fatty acid, oxidized low density lipoprotein (LDL), neutrophil elastase, and hyaluronan (13). However, representative danger signals are as yet still poorly defined in endometriosis. These endogenous ligands might be danger signals activating NF-kappaB inflammasome via TLR in development and progression of endometriosis. These molecular targets may be useful for the development of novel strategies for therapy of endometriosis.

Although endometriosis generally remains a benign condition, it demonstrates somatically acquired genetic alterations (2). The majority of endometriotic cyst glands are monoclonal in origin (14.15). In the case of multifocal lesions, each focus originates monoclonally, and multifocal lesions are the apparent independent origins (16). The monoclonality of endometriotic lesions suggests that they may carry neoplastic potentials (16). Recent molecular findings in endometriosis include loss of heterozygosity (LOH) in the majority of cases associated with ovarian carcinoma (17).

4. EPITHELIAL OVARIAN CARCINOMA (EOC)

4.1. Risk factors

There are several theories to explain the epidemiology of EOC (18). Epidemiologic studies support the following notion. Increasing the risk of EOC includes low parity, infertility, hormonal factors, early age of menarche, late age of menopause, persistent inflammatory status, selected inflammatory gene polymorphisms, genetics, and exposure to certain environmental agents such as talc, pesticides, and herbicides (18). Endometrial and breast carcinomas are also associated with these risk factors (19). Other investigators also demonstrated that risk of EOC is associated with perineal use of talc and with a history of endometriosis, pelvic inflammatory disease, or hyperthyroidism (20,21). The inflammation hypothesis

proposes that these factors may predispose to inflammation and irritation. Although some investigators speculated that drugs used in the process of *in vitro* fertilization appear to be associated with increased risk for gynecological carcinoma, subsequent studies demonstrated no increased risk for ovarian carcinoma after IVF treatment (19).

Currently, there is no proven relationship between any type of gynecological carcinoma and drugs used for infertility treatment (22). Interestingly, oral contraceptive use is associated with a decreased risk of EOC and may operate through preventing the trauma from incessant ovulation (23). Tubal ligation also prevents retrograde menstruation and it has been shown to be protective from EOC (18,24).

4.2. Molecular genetics

EOC are a heterogeneous group of neoplasms. Genetic studies support this notion. The model of malignant transformation involves the stepwise introduction of genetic alterations, which confers a clonal selective advantage, predisposing to the next step including initiation, promotion and progression. This is often accompanied by activation of protooncogenes to oncogenes and also inactivation of tumor suppressor genes by methylation, mutation or deletion. Most neoplasms are monoclonal in origin and evidence for monoclonality of endometriosis has been demonstrated in several studies (16,17). Current data indicate that EOC can be divided into two broad categories based on their clinical pattern of tumor progression, morphologic and molecular genetic changes (25,26,27,28). Type I EOC include low-grade serous adenocarcinoma (SAC), low-grade endometrioid adenocarcinoma (EAC), mucinous adenocarcinoma (MAC), and a subset of clear cell carcinomas (CCC). Type II EOC include high-grade SAC, high-grade EAC, undifferentiated carcinoma, and probably some CCC. It is likely that most low-grade EOC arise from pre-existing cystadenoma or endometriosis in a stepwise fashion in an adenoma-borderline tumor-carcinoma sequence (25,26). Low-grade SAC probably arise via activation of the RAS-RAF signaling pathway secondary to mutations in KRAS and BRAF (25). MAC have a high prevalence of KRAS mutations and arise via an adenoma-carcinoma sequence (25). High-grade SAC might arise from the ovary, fallopian tube or peritoneum without an easily identifiable precursor lesion, and is the most clinically important histological subtype of EOC (25). High-grade SAC and possibly EAC arise with TP53 mutations and dysfunction of BRCA1 and/or BRCA2 (25). More recent analysis showed that mutant TP53 is a driver mutation in the pathogenesis of high-grade SAC (29). Mutations of CTNNB1 (catenin [cadherin-associated protein], beta 1) are observed most frequently in EAC (26). Mutations of PIK3CA (the catalytic subunit of PI3K [phosphoinositide 3-kinase]) are also common in CCC (30).

5. RISK OF DEVELOPING EOC AMONG WOMEN WITH ENDOMETRIOSIS

5.1. Epidemiology

We investigate whether endometriosis-associated ovarian carcinoma is a specific entity compared with EOC not associated with endometriosis, with respect to epidemiology, natural history, etiology and pathogenesis. We also review the risk of developing EOC among women with endometriosis. Data from large cohort and case-control studies have linked endometriosis to an increased risk of EOC (1,22,31,32,33,34,35,36). A cohort study from Canada indicated that endometriosis represents a serious risk factor for developing EOC and suggested an early onset of EOC in women having endometriosis of about 5 years average (31). There are two cohort studies from Sweden: Swedish population study demonstrated that the risk of EOC was increased 4.2-fold in the presence of endometriosis, irrespective of whether endometriosis is distant or adjacent to EOC (1). National Swedish Inpatient Data also showed that endometriosis is linked to elevated risks for not only EOC but also breast carcinoma, renal carcinoma, thyroid carcinoma, brain tumors, and malignant melanoma (34). More recent two studies reported three- (35) to eight-fold (36) increase risk of EOC in women with a history of endometriosis, with a lesser risk increase among women who underwent subsequent ovarian surgery (35). Several clinical series also reported that CCC and EAC are the most frequent types of EOC associated with endometriosis (18,22,32).

The exact cause remains unknown, but the incidence of CCC has been steadily increasing in Japan (37). They comprise approximately 20% of all EOC (37). CCC is a clinically and pathologically distinct entity among EOC, recognized for its resistance to standard platinum-based chemotherapy at advanced stage disease and poor prognosis (38). Therefore, in Japan, more studies are needed to establish risk factors that may lead to malignant transformation of this condition and to identify predisposed individuals who may require closer surveillance (18).

Somigliana *et al.* reported that endometriosis is associated with an increased risk of EOC, but data indicate no increased risk of carcinomas in general. (33). However, Brinton *et al.* showed an increased risk of extra-pelvic carcinomas (breast and non-Hodgkin's lymphoma) in women with endometriosis (1). Recent report also indicated that evidence for an association with melanoma and non-Hodgkin's lymphoma is increasing in the presence of endometriosis (33). Japanese study could not observe overall association between genetic variation of melanoma and non-Hodgkin's lymphoma and risk of endometriosis or EOC (36).

Taken together, endometriosis has been believed to increase the risk of developing EOC. Endometriosis and EOC share many common predisposing factors (18). Both conditions demonstrate similar patterns regarding invasion and metastasis. They respond similarly to estrogen-induced growth signaling, express resistance to apoptotic mechanisms, and are characterized by genetic abnormalities (18).

5.2. Morphology

Pathologists often observed malignant transformation of endometriosis to CCC or EAC, via the step of atypical endometriosis (39,40). Histopathology

showed that endometriosis displays features of atypia, atypical endometriosis, which has been observed in 10–40% of ovarian endometriosis (41). Some cases show direct continuity of the atypical ovarian endometriosis with EOC. Atypical endometriosis shows proliferation activity intermediate to those of typical endometriosis and EOC, suggesting it is a precancerous status (32,40). Severe atypia may be associated with aneuploidy (2). These findings support the histological observations that CCC and EAC might arise through malignant transformation of endometriotic lesions (2,42). CCC and EAC are the commonest EOC with ovarian endometriosis, while CCC and adenosarcoma are the commonest EOC in extra-ovarian endometriosis (43).

5.3. Molecular genetics

There is clinical evidence to support that endometriosis (by definition a benign process) could simultaneously have the potential for malignant transformation (18). Endogenous or exogenous hyperestrogenism was positively related to the risk of development of carcinoma from endometriosis (1,44). Significantly, both carcinoma and endometriosis share some of the mediators implicated in this 'inflammatory angiogenesis' model. Furthermore, these mediators exhibit genetic polymorphisms of several genes, including intercellular adhesion molecule-1 (ICAM-1), IL-6 and IL-10 gene promoters, tumor necrosis factor (TNF)-alpha, NF-kappaB, and peroxisome proliferator-activated receptor (PPAR)-gamma genes, that predispose either to endometriosis or to carcinoma (45).

Transformation of a normal cell to a malignant one requires phenotypic changes associated with each of the initiation, promotion and progression phases of the carcinogenic process through a number of genetic alterations (46,47). Genes in each of these phases acquire alterations in their transcriptional activities that are associated either with hypermethylation or hypomethylation (47). According to some allelotyping studies, endometriotic cells displayed a somatically acquired methylation, mutation, or deletion in chromosomal regions supposed to contain genes involved in ovarian carcinogenesis (15). Tumor suppressor genes are commonly altered in EOC, and the development of endometriosis may involve alterations in the same class of genes (14). Although the morphologic data strongly support an origin of CCC from endometriosis, very little is known about the molecular genetic mechanisms that are involved in clear cell tumorigenesis (25,38).

5.3.1. Loss of heterozygosity (LOH)

Cases with EOC arising from endometriosis showed common genetic LOH alterations in endometriosis and carcinoma, indicating a possible malignant genetic transition spectrum between endometriosis and EOC (42,48). LOH studies have implicated the involvement of specific chromosomal regions (1p, 3p, 5q, 8p, 9p, 10q, 11q, 13q, 17q and 22q) (37,49). Inactivation of tumor suppressor genes may play a role in the development of a subset of cases (14). Tumor suppressor gene mapping to these chromosomal regions, such as von Hippel-Lindau (VHL) on 3p, adenomatous polyposis coli (APC) on 5q, and ataxia telangiectasia mutated (ATM) on 11q (50,51,52). These data suggest that both lesions were consistent with a common genetic lineage.

5.3.2. K-ras and PTEN

Mutations and deletions of PTEN tumor suppressor gene have been found in about 20% of ovarian endometriosis (15). It has been reported that reduced expression of PTEN may be involved in the malignant evolution of endometriosis (53), and that inactivation of the PTEN gene is an early event in the development of EAC and CCC (54).

Moreover, a model of genetically engineered mice harboring an oncogenic allele of K-ras resulted in development of endometriosis, and then a deletion of PTEN caused the progression towards the EAC tumor (15). In humans, however, K-ras mutations were detectable in CCC but not in endometriosis or atypical endometriosis (46). Therefore, it is possible that K-ras mutations are associated with malignant transformation of atypical endometriosis into CCC, although further research is needed to define this mechanism (46). In humans, low-grade EAC reportedly arise from endometriosis via mutations in CTNNB1 (25). Based on these data, the causal link between endometriosis and EAC remains to be defined in terms of underlying molecular mechanisms (15).

The molecular basis of the pathway from endometriosis to CCC has been described, i.e., genetic instability or DNA aneuploidy in endometriotic lesions, with mutation or deletion of PTEN (2,14,42,54). Furthermore, not only PTEN (early event) but also multiple genes such as APC, p53, polo-like kinases, Emi1 and K-ras (late event) genes may be involved in CCC carcinogenesis (37). Interestingly, K-ras mutations may also be associated with malignant transformation of endometriosis into CCC (39).

5.3.3. P53

Mutant TP53 is specific for the pathogenesis of high-grade SAC. p53 mutation was observed in 30% of endometriosis coexisting with CCC, whereas no mutations were detected in solitary endometriosis, atypical endometriosis, or endometriosis coexisting with EAC (41,55). Some genetic alterations, which induce p53 mutations in a subset of endometriosis, may affect malignant transformation of endometriosis into CCC (55). However, mutant TP53 is not specific for the pathogenesis of CCC.

5.3.4. Hepatocyte nuclear factor (HNF)-1beta

Recent studies based on genome-wide expression analysis technology have noted that hepatocyte nuclear factor (HNF)-1beta was positive in all of the clear cell components (56) possibly through hypomethylation (57). Specific expression of HNF-1beta was observed in endometriosis and CCC, suggesting that early differentiation into the clear cell lineage takes place in endometriosis (37). The HNF-1beta-dependent pathway of CCC was analyzed, which is providing new insights into

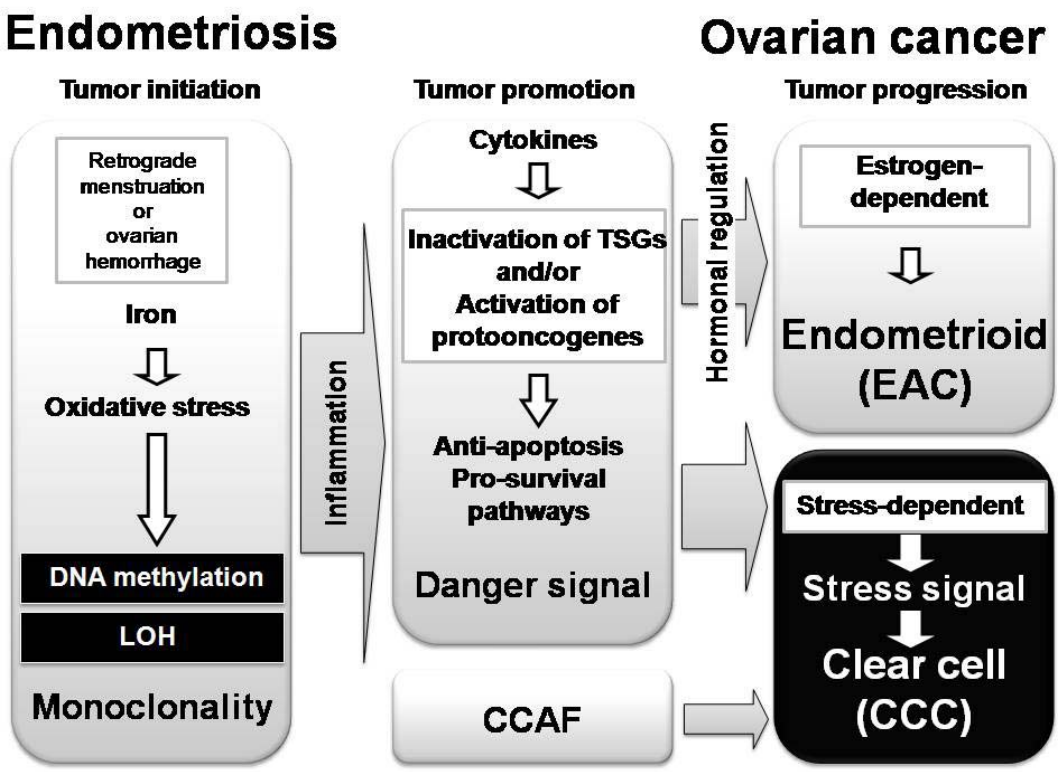

Figure 1. A possible novel model shows the pathogenesis of endometriosis-associated epithelial ovarian carcinoma (EOC). The pathogenesis of endometriosis is multifactorial. Retrograde menstruation or ovarian hemorrhage carries high concentrations of heme and iron into the peritoneal cavity or ovarian endometrioma. The inflammatory response may play a role in the pathogenesis of endometriosis possibly through iron-mediated oxidative stress. TLR-mediated inflammation might be critical to the signaling of a variety of "danger signals". The cytokines can cause unregulated mitotic division, growth, migration, and differentiation. Endometriotic cells displayed a somatically acquired methylation, mutation, or deletion in chromosomal regions (LOH) supposed to contain genes involved in ovarian carcinogenesis. Thus, the majority of endometriotic cyst glands are monoclonal in origin. Tumor suppressor genes are commonly altered in this situation, and the development of endometriosis-associated EOC may involve alterations in the same class of genes. Reductions in ER and PR expression were observed with progression from endometriosis to atypical endometriosis in CCC specimens. EAC may develop from atypical cells in the setting of excess estrogenic stimulation. In contrast, CCC may occur under the stress signaling pathways, which results in accumulation and overexpression of HNF-1beta. The HNF-1beta-dependent pathway enhances anti-apoptosis and glycogen synthesis and resistance of CCC to anticancer agents. A subset of CCC may arise in association with CCAF. These data allow us to speculate that CCC and EAC have some shared as well as some distinct risk factors, and should be considered separately in studies of endometriosis-associated EOC.

regulation of apoptosis and glycogen synthesis and resistance of CCC to anticancer agents (37). This review summarizes recent advances in HNF-1beta and its target genes; the potential challenges to the understanding of carcinogenesis, pathogenesis, and pathophysiology of CCC; and a possible novel model is proposed (37). The molecular pathology of CCC is heterogeneous and multiple pathways of development, possibly via genetic alteration by oxidative stress (see below).

5.3.5. Redox (Reduction and Oxidation)

Iron is essential to almost all forms of life. It is an essential metal in mammals for oxygen transport by hemoglobin and for the function of many enzymes including catalase and cytochromes (58). Redox cycling is a characteristic of transition metals such as iron (58). Excess iron is potentially toxic as its catalytic activity induces the generation of reactive oxygen species (ROS) (58).

Retrograde menstruation or ovarian hemorrhage carries highly pro-oxidant factors, such as heme and iron, into the peritoneal cavity or ovarian endometrioma (7) (Figure 1). Blood coagulation and hemolysis occurring during the development of endometriosis result in high levels of free heme and iron. Free iron is observed *in situ*ations such as in endometriotic cysts (58). Recent studies based on genome-wide expression analysis technology have noted specific expression of heme/iron-dependent mediators in endometriosis (7). Several important endometriosis-specific genes overlap with those known to be regulated by iron. Other genes are involved in oxidative stress (7). It is also known that ROS or

superoxide can release free iron from ferritin and hemosiderin (58). Endometriotic lesions are rich in hemosiderin-laden macrophages. In addition to genetic damage via the oxidative mechanism, oxidative stress can also cause significant changes in DNA methylation and histone modifications, leading to epigenetic silencing or reactivation of gene expression (47). Thus, free iron is quite cytotoxic as well as mutagenic and carcinogenic (58). A histologically normal ectopic endometrium might bear genetic damages caused by free iron-dependent oxidative stress (7).

Iron compounds were first reported to induce sarcomas in rats by Richmond in 1959 (58). Thereafter, several iron-induced carcinogenesis models were established (58,59,60,61). In humans, genetic hemochromatosis and asbestosis are two major diseases associated with iron-induced carcinogenesis (58). The heme/iron-dependent signaling pathway of endometriosis is providing new insights into the regulation of inflammation, detoxification, and survival of endometriosis as well as the elucidation of molecular genetics for development of endometriosis-associated EOC.

5.3.6. Estrogen receptors (ER) and Progesterone receptor (PR)

EOC can express both estrogen receptors (ER) and progesterone receptors (PR) (62). The ER positivity was lower in endometriosis-associated EOC than that in EOC without endometriosis (63). Many investigators showed that the characteristic immunoprofile for CCC was negativity or weakly positivity for ER and negativity for PR (64,65,66). Reductions in ER and PR expression were observed with progression from endometriosis to atypical endometriosis in CCC specimens (67). Exceptionally, one paper showed that CCC showed positivity with ER (70%) and PR (60%) (68). In general, however, ER and PR expression is present in a minority of CCC and disappearance of hormone dependency might therefore be associated with malignant transformation to CCC (67).

5.3.7. Wilms' tumor suppressor gene (WT1)

The Wilms' tumor suppressor gene (WT1), a nuclear transcription factor, plays a role in the organogenesis of the genitourinary tract and mesothelium, as well as Wilms' tumors (69). Most SAC of the ovary and peritoneum, mesotheliomas, and Wilms' tumor have been shown to express WT1 (69). WT1 protein regulates the expression of the insulin-like growth factor (IGF) and transforming growth factor (TGF) systems, both of which are implicated in tumorigenesis and angiogenesis (70). A diagnostic panel consisting of WT1, ER, and HNF-1beta is useful for distinguishing CCC from high grade SAC (71,72). SAC tissues expressed WT1 and ER, although expression of these genes was lacking in CCC (73). Conversely, CCC expressed HNF-1beta, but not WT1 and ER, since the WT1 promoter was methylated in CCC (73).

5.3.8. Microsatellite instability (MSI)

The chronic oxidative stress-induced inflammatory processes may be involved in carcinogenesis possibly through DNA methylation or damage. The association between increased DNA-methyltransferase (DNMT) activity and tumor development suggest a fundamental role for this enzyme in the carcinogenesis and progression. The DNMT-related genes were overexpressed in endometriosis, providing that endometriosis is an epigenetic disease and aberrant methylation is rampant (74). For example, hypermethylation of hMLH1, with concurrent absence of protein expression, is noted in ~10% of endometriotic lesions (53). Reduced expression of hMLH1 may be involved in the malignant evolution of some endometriosis tissues (53).

5.3.9. Anti-apoptosis and survival

Malignancy commonly displays not only p53 gene inactivation but also overexpression of anti-apoptotic (Bcl-2) and underexpression of pro-apoptotic (BAX) factors. Bcl-2 was reported to stain 23% of endometriotic cysts, 67% of EAC, 73% of CCC (75), suggesting that alterations in Bcl-2 may be associated with the malignant transformation of endometriosis. When endometriosis is associated with CCC, there is a change of its cytokine production that inhibits cell growth (76). The proliferating cell nuclear antigen (PCNA) labeling index was lower in endometriosis-associated EOC compared to EOC without endometriosis (76). The destruction of the surrounding matrix by endometriosis and CCC might be caused by various matrix metalloproteases (MMPs), which are mainly produced in stromal cells (77).

5.3.10. Chemoresistance

CCC is known to be highly resistant to platinum-based chemotherapy (78,79). Enhanced expression of detoxification genes, including UGT1A1, ANXA4, ASK1, GPX3, GLRX, SP17, and SOD2, was identified in CCC cells using gel electrophoresis and mass spectrometry, real-time RT-PCR, Western blot, or immunohistochemical analysis (78,79,80,81). Annexin A4 (ANXA4) confers chemoresistance in EOC cells by enhancing drug efflux (78). Uridine diphosphate glucuronosyltransferase isoform 1A1 (UGT1A1) genotype has been reported to be associated with time to progression and survival in patients treated with irinotecan (82). Furthermore, sperm protein 17 (SP17) has been identified as a candidate gene related to the chemoresistance of CCC (80). These detoxification enzymes specifically overexpressed in CCC are associated with chemoresistance (37).

6. CCC ARISING FROM CLEAR CELL ADENOFIBROMA

The pathogenesis of CCC involves two putative precursor lesions: endometriosis and clear cell adenofibroma (CCAF). CCAF components co-existed in 21% of surgically resected CCC (83). CCC with CCAF components shows several distinct clinicopathological characteristics, e.g., a lower frequency of co-existing endometriosis (83), a higher frequency of low-grade tumor, a lower cell proliferative activity, and better patient prognosis (83,84). The PDGF pathway is active in a subset of CCC. Positivity for PDGF and its receptors increased in accordance with increased atypia in CCAF co-existing with CCC (83). However, in contrast, PDGF expression

decreased in accordance with increased atypia in endometriosis co-existing with CCC (85). These clinical and genetic data suggest biological differences between CCC that arise in association with CCAF versus endometriosis.

7. A POSSIBLE NOVEL MODEL ON MOLECULAR GENETICS

CCC and EAC have some shared as well as some distinct risk factors, and should be considered separately in studies of endometriosis-associated EOC (24). The repeated events of hemorrhage in endometriosis can contribute to carcinogenesis and tumor progression via 3 major processes: 1) increasing oxidative stress induced by free iron promotes DNA methylation and mutagenesis thus contributing to tumor initiation; 2) activating pro-survival and anti-apoptotic pathways contribute to tumor promotion; and 3) by creating an environment that supports sustained growth, angiogenesis, migration, and invasion of tumor cells, thus supporting tumor progression. Process 1 implies that LOH caused by chronic oxidative stress is a critical factor. Endometriotic lesions are monoclonal in origin and suggest their neoplastic potential. Process 2 shows that inactivation of tumor suppressor genes and/or activation of oncogenes are relatively an early event in the development of endometriosis-associated EOC (EAC and CCC) in the carcinogenic process, in particular tumor promotion. In Process 3, endometriosis-associated EOC may be divided into two groups, reflecting differences in clinical behavior and pathogenesis. EAC typifies the one group of endometriosis-associated EOC that develop from atypical cells in the setting of excess estrogenic stimulation. In contrast, CCC are representative of another endometriosis-associated EOC that occur under the estrogen-independent pathways in women who lack the typical carcinoma risk factors. CCC are frequently associated with aberrant expression of stress signaling pathways, which results in accumulation and overexpression of HNF-1beta. The HNF-1beta-dependent pathway enhances anti-apoptosis and glycogen synthesis and resistance of CCC to anticancer agents. In a case of advanced stage, these highly aggressive CCC tumors account for a disproportionate number of EOC deaths. The present review integrates clinical and basic research observations in an attempt to provide a comprehensive understanding of how repeated events of hemorrhage and subsequent chronic inflammation and oxidative stress processes may contribute to EOC development in endometriosis patients.

The malignant potential of endometriosis holds serious implications for management, such as the need for surgical intervention for complete disease treatment (8). The definition of key molecules that are important for stress signaling opens the possibility to develop new drugs to combat endometriosis-associated EOC. This review summarizes recent advances in the understanding of epidemiology, carcinogenesis, pathogenesis, and pathophysiology of endometriosis-associated EOC; and a possible novel model is proposed.

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